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Article

Phenolic compounds from geopropolis of *Melipona fasciculata* smith inhibit the proliferation of lung cancer cells

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Geopropolis produced by the stingless bee *Melipona fasciculata* was investigated for its potential anticancer properties. A hydroethanolic extract was separated via liquid–liquid partitioning into hexane (HF), ethyl acetate (EAF), and hydromethanolic (HMF) fractions. Bioassay-guided chromatographic fractionation of the EAF yielded 13 subfractions (FRGE-1 to FRGE-13). The most active subfractions were analyzed by LC and LC-ESI/IT-MS/MS. Cytotoxicity was evaluated using the MTT assay in lung cancer cell lines (H460 and A549) and normal endothelial cells (HUVEC), and the selectivity index (SI) was subsequently calculated. All three fractions (HF, EAF, HMF) inhibited lung cancer cell proliferation after 48 h. Subfractions FRGE9 and FRGE11 exhibited selective cytotoxicity, demonstrating over threefold higher activity in tumor cells than in normal cells. Phenolic compounds identified in FRGE9 included dihydroxybenzoic acid, apigenin-6-C-glucoside, and luteolin-7-O-rutinoside, while FRGE11 contained diosmetin and myricetin-3-galactoside. These compounds are being reported for the first time in the geopropolis of *M. fasciculata*. The results suggest these molecules may serve as prototypes for developing safer and more effective lung cancer therapeutics.

Keywords: Cytotoxicity. Lung cancer. Chemical composition. Bee products.

INTRODUCTION

Lung cancer remains a leading cause of cancer-related mortality worldwide (American Cancer Society, 2018; Bray *et al.*, 2018). Treatment is hindered primarily by resistance to antineoplastic agents and associated toxicity (Lim, Ma, 2019; Liu *et al.*, 2024). In Brazil, the National Cancer Institute (2025) projects approximately 32,560 new cases diagnosed annually between 2023 and 2025.

Natural products of animal origin, particularly those derived from stingless bees, have gained attention as potential sources of new molecules and adjuvant therapies for cancer. Several studies have demonstrated the healing, antioxidant, anti-inflammatory, and antitumor properties of propolis and geopropolis, supporting their relevance in oncological research (Lavinas *et al.*, 2019; Al-Hatamleh *et al.*, 2020; Nainu *et al.*, 2021; Campos *et al.*, 2021; Pereira *et al.*, 2021; Reis *et al.*, 2025).

The stingless bee *Melipona fasciculata* Smith (Hymenoptera: Apidae: Meliponini), known locally as "tiúba," produces honey, pollen, wax, and geopropolis—a mixture of plant resins, secretions, wax, and soil used to protect the hive, regulate temperature, and prevent microbial invasion (NogueiraNeto, 1997).

Prior research on the hydroethanolic extract of *M. fasciculata* geopropolis has shown antitumor activity against canine osteosarcoma cells (Cinegaglia *et al.*, 2013), cytostatic effects against human laryngeal carcinoma (Araújo *et al.*, 2015), and synergistic effects with several chemotherapeutics (Bartolomeu *et al.*, 2016). Reduced viability in leukemic cells was also observed (Oliveira *et al.*, 2016).

Our group has also shown that ovarian and lung cancer cells are sensitive to the hydroethanolic extract of *M. fasciculata* geopropolis. We identified triterpenes, triterpenic saponins, flavonoids, and aromatic acids

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in these extracts (Barboza *et al.*, 2020). However, no studies have examined the antitumor activity or chemical profiles of apolar and polar fractions obtained by liquid–liquid partitioning of the hydroethanolic extract.

Recognizing the significant impact of lung cancer, this study examines the cytotoxicity of ethyl acetate subfractions from *M. fasciculata* geopropolis on A549 and H460 lung cancer cells and on HUVECs, and characterizes the chemical profiles of the most active subfractions.

MATERIAL AND METHODS

Geopropolis Samples

Geopropolis samples were collected in 2018 from a meliponary in Viana, Maranhão, Brazil (03°13'13'' S, 45°00'13'' W). Material was removed using a sterile spatula, stored at 4°C, and registered in SISGEN (code ABCEA59).

Extraction

The geopropolis (200 g) was finely ground and macerated in 70% ethanol for 6 days (1:5 w/v), with solvent renewal every 48 h. The extract was filtered, concentrated under reduced pressure at 40 °C, and lyophilized to obtain the hydroethanolic extract (EHGV).

Liquid–liquid Partitioning

EHGV was dissolved in methanol:water (1:1 v/v) and partitioned with hexane and ethyl acetate, yielding the hexane fraction (HF), ethyl acetate fraction (EAF), and hydromethanolic fraction (HMF). Fractions were dried and concentrated, and their yields were calculated.

Y (Total extract yield in %) = Wext (weight of dry extract in g)/Wgeo (weight of fresh geopropolis samples in g) × 100

Chromatographic Fractionation

A 1.2 g sample of EAF was subjected to silica gel column chromatography. Sequential eluents were hexane, hexane/ethyl acetate, ethyl acetate/methanol, and methanol. Eighty-four fractions were collected and pooled by TLC similarity into 13 subfractions labeled FRGE-1 to FRGE-13.

LC–ESI/IT–MS/MS Analysis

The bioactive subfractions FRGE9 and FRGE11 were analyzed using LCESI/ITMS/MS with a Gemini C18 column. Elution used a water/formic acid (0.1%) and methanol gradient. Identification was based on mass fragmentation patterns.

Cell Culture

Lung cancer cell lines (H460, A549) and normal endothelial cells (HUVEC) were obtained from ATCC and cultured in RPMI supplemented with 10% FBS and antibiotics at 37 °C, 5% CO_2.

Cytotoxicity Assay

Fractions and subfractions were tested at concentrations of 15.62–250 µg/mL for 48 h using the MTT assay (Mosmann, 1983). Absorbance was measured at 538 nm.

Selectivity Index

Selectivity index (SI) was calculated as:

$SI = IC_{50}$ (normal cells) / IC_{50} (tumor cells)

Values ≥ 2.0 were considered indicative of selective toxicity.

Statistical Analysis

Data were presented as mean ± SD and normalized and log-transformed. Non-linear regression determined

IC_{50} values. Two-way ANOVA followed by Dunnett's test was used ($p < 0.05$).

RESULTS

Fraction Yields

Despite strong cytotoxicity, the hexane fraction (HF) had a low yield (4%), making it unsuitable for further study. The hydromethanolic (HMF, 30%) and ethyl acetate (EAF, 26%) fractions had higher yields. All three fractions were obtained by liquid–liquid partitioning of the hydroethanolic extract (EHGV).

Cytotoxicity of Crude Fractions (HF, EAF, HMF)

All three fractions were evaluated against lung cancer cell lines (H460 and A549) and normal endothelial cells (HUVEC). HF exhibited the strongest cytotoxic effect, with IC_{50} values of 40.99 µg/mL (H460) and 51.83 µg/mL (A549). EAF showed moderate activity (118.70 µg/mL and 142.10 µg/mL), while HMF demonstrated weaker cytotoxicity (196.50 µg/mL and 275.90 µg/mL). Importantly, all fractions showed low toxicity toward normal cells ($IC_{50} > 250$ µg/mL) (Table I).

TABLE I – Inhibitory concentration (IC_{50}) of the hexane fraction (HF), ethyl acetate fraction (EAF), and hydromethanolic fraction (HMF) obtained from the lyophilized hydroethanolic extract of geopropolis from *Melipona fasciculata* Smith (EHGV) on the proliferation of lung cancer cell lines (H460 and A549) and normal cells (HUVEC) after 48 h

Samples		Cell lines	
	H460	A549	HUVEC
HF	40,99 µg/mL	51,83 µg/mL	>250 µg/mL
EAF	118,70 µg/mL	142,1 µg/mL	>250 µg/mL
HMF	196,50 µg/mL	275,9 µg/mL	>250 µg/mL

HF = Hexane fraction. EAF = Ethyl acetate fraction. HMF = Hydromethanolic fraction. IC_{50} values were calculated using a non-linear regression equation: log (inhibitor) versus response variable slope, by the MTT assay—concentration required to inhibit cell growth by 50% as determined from the dose-response curve. Values are expressed as the mean of cytotoxicity assays (n = 3).

Cytotoxicity of EAF Subfractions (FRGE-1 to FRGE-13)

Fractionation of EAF produced 13 subfractions. As shown in Table II, most subfractions had moderate to weak cytotoxicity. FRGE-9 and FRGE-11 had pronounced activity against A549 cells, with IC_{50} values of 65.52 µg/mL and 63.87 µg/mL, respectively, and limited toxicity toward normal HUVEC cells.

FRGE-6, FRGE-7, and FRGE-8 were selective for H460 cells. FRGE-9 and FRGE-11 showed selective toxicity toward A549 cells.

TABLE II – Inhibitory concentration (IC_{50}) of the subfractions FRGE-1 to FRGE-13 for the proliferation of lung cancer cell lines (H460 and A549) and normal cells (HUVEC) after 48 h

Samples		Cell lines	
	H460	A549	HUVEC
FRGE-1	146.40 µg/mL	128.50 µg/mL	129.70 µg/mL
FRGE-2	133.60 µg/mL	125.80 µg/mL	58.82 µg/mL
FRGE-3	141.60 µg/mL	161.70 µg/mL	75.78 µg/mL
FRGE-4	79.20 µg/mL	138.70 µg/mL	115.20 µg/mL
FRGE-5	87.13 µg/mL	175.50 µg/mL	88.83 µg/mL
FRGE-6	86.50 µg/mL	>250 µg/mL	177.30 µg/mL
FRGE-7	88.58 µg/mL	251.10 µg/mL	>250 µg/mL
FRGE-8	112.60 µg/mL	172.50 µg/mL	>250 µg/mL
FRGE-9	>250 µg/mL	65.52 µg/mL	216.10 µg/mL
FRGE-10	178.80 µg/mL	>250 µg/mL	192.10 µg/mL
FRGE-11	>250 µg/mL	63.87 µg/mL	215.40 µg/mL
FRGE-12	>250 µg/mL	>250 µg/mL	120.30 µg/mL
FRGE-13	239.00 µg/mL	>250 µg/mL	168.50 µg/mL

FRGE-1 to FRGE-13 = Subfractions obtained from the chromatographic fractionation of the ethyl acetate fraction (EAF) of the lyophilized hydroethanolic extract of geopropolis from *M. fasciculata* (EHGV). IC_{50} values were calculated using a non-linear regression equation: log (inhibitor) versus response variable slope, by the MTT assay—concentration required to inhibit cell growth by 50% as determined from the dose-response curve. Values are expressed as the mean of cytotoxicity assays (n = 3).

At 62.5 µg/mL, HF inhibited A549 and H460 lung cancer cell proliferation by less than 40% (Figure 1A–B), and similarly, FRGE-1 to FRGE-4 at 250 µg/mL did not exceed this inhibition threshold (Figure 1D), indicating limited antiproliferative potential of these initial subfractions. In line with this, HF, EAF, and HMF, as well as FRGE-1 to FRGE-4, which unlike the more active subfractions did not display significant cytotoxicity toward A549 cells (Figure 1E), maintained cell viability in normal HUVEC cultures (Figure 1C), demonstrating their preferential activity toward tumor cells.

In H460 cells, FRGE-3 and FRGE-4 at 250 µg/mL produced growth inhibition below 40% (Figure 1G), while FRGE-5 and FRGE-8 resulted in less than 20% inhibition at the same concentration (Figure 1H). In contrast, FRGE-9 and FRGE-11 exhibited distinctly stronger cytotoxicity in A549 cells, with IC_{50} values close to 63 µg/mL (Figure 1F), although their effect on H460 cells was comparatively weaker (Figure 1I). Importantly, even these most active subfractions preserved HUVEC viability at 62.5 µg/mL (Figure 1L), and none of the subfractions from FRGE-1 to FRGE-8 exhibited relevant cytotoxicity in normal cells up to 31.25 µg/mL (Figure 1J–K), reinforcing their favorable safety profile.

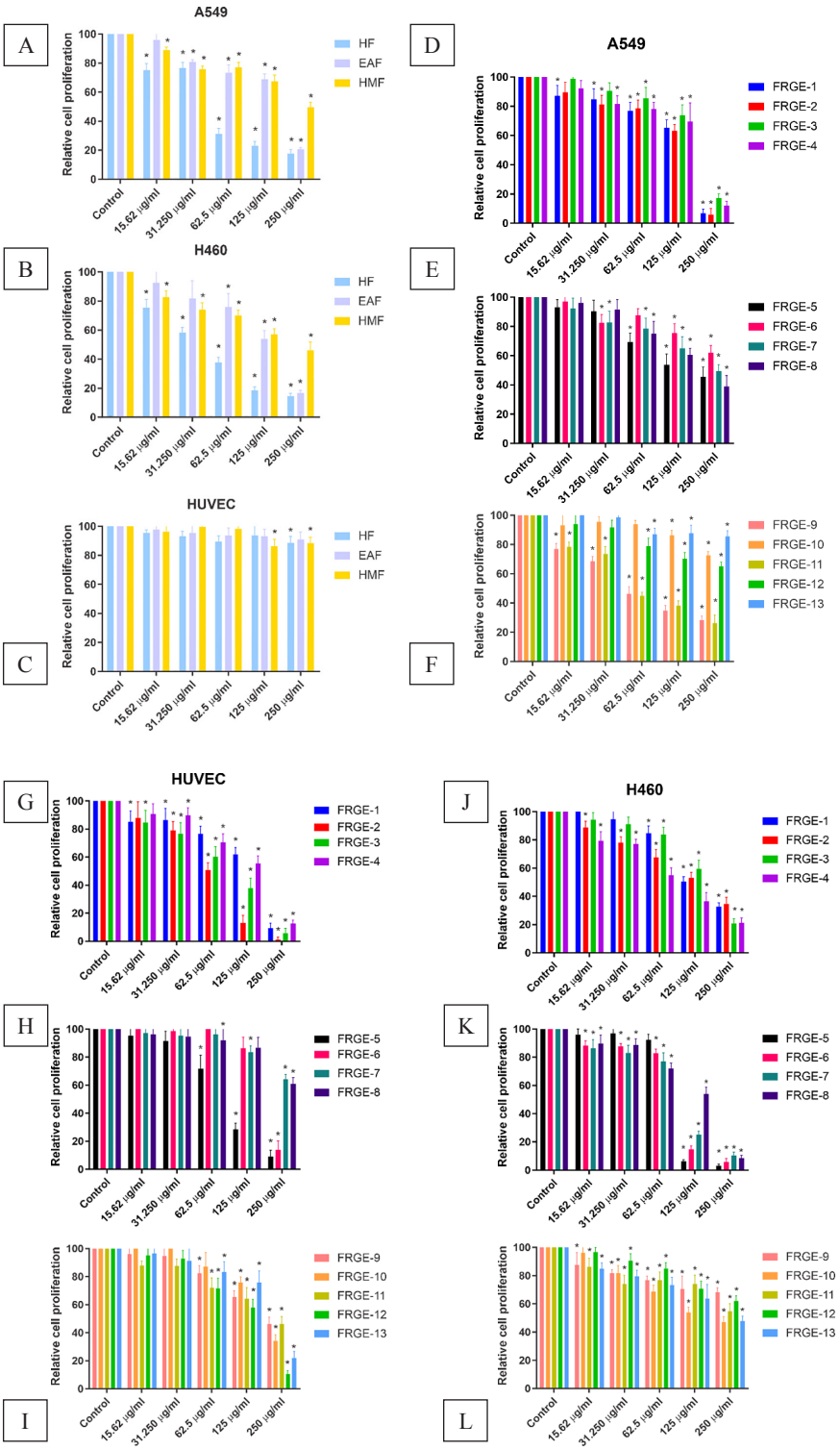


FIGURE 1 – Effects of HF, EAF, and HMF on lung cancer cell lines (A549 (A) and H460 (B)) and on normal endothelial cells (HUVEC (C)) after 48 h; effects of FRGE-1 to FRGE-4 (D), FRGE-5 to FRGE-8 (E), and FRGE-9 to FRGE-13 (F) on A549 cells after 48 h; and corresponding effects on H460 (G–I) and HUVEC (J–L) cell lines after 48 h. Data were analyzed using two-way ANOVA followed by Dunnett's test. *p ≤ 0.05 was considered statistically significant.

Selectivity Index (SI)

SI analysis showed that HF had the highest selectivity for both H460 (SI > 6.09) and A549 (SI > 4.82), as presented in Table III. Among subfractions, FRGE-6, FRGE-7, and FRGE-8 had SI ≥ 2.0 for H460, while FRGE-9 and FRGE-11 reached SI values of 3.29 and 3.37 for A549, indicating preferential action on tumor cells.

TABLE III – Selectivity index (SI) of fractions and subfractions of the lyophilized hydroethanolic extract of geopropolis from *Melipona fasciculata* Smith

Samples	Cells	
	H460	**A549**
HF	>6.09	>4.82
EAF	>2.10	>1.75
HMF	>1.27	>0.90
FRGE-1	0.88	1.00
FRGE-2	1	0.5
FRGE-3	0.43	0.46
FRGE-4	1.45	0.83
FRGE-5	1.01	0.50
FRGE-6	2.04	<0.70
FRGE-7	>2.82	>0.99
FRGE-8	>2.22	>1.44
FRGE-9	<0.86	3.29
FRGE-10	1.07	<0.76
FRGE-11	<0.86	3.37
FRGE-12	<0.48	<0.48
FRGE-13	0.70	<0.67

HF = Hexane fraction. EAF = Ethyl acetate fraction. HMF = Hydromethanolic fraction. FRGE-1 to FRGE-13 = Subfractions obtained from the chromatographic fractionation of the ethyl acetate fraction (EAF) of the lyophilized hydroethanolic extract of geopropolis (EHGV).

Chemical Characterization

Considering that the FRGE-09 and FRGE-11 subfractions were the most active in the anticancer assays, HPLC/UV-vis and LC analyzed their chemical compositions–ESI/IT–MS/MS.

The HPLC chromatograms of the most bioactive subfractions are shown in Figures 2 and 3. HPLC and LC–ESI/IT–MS/MS analyses identified key phenolic compounds, including diosmetin, apigenin-6-C-glucoside, luteolin-7-O-rutinoside, and myricetin-3-galactoside (Tables IV and V). These compounds are reported here for the first time in the geopropolis of *Melipona fasciculata*.

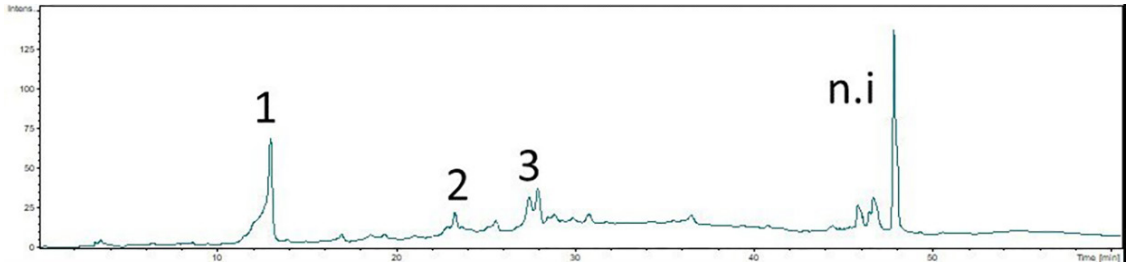


FIGURE 2 – HPLC chromatogram of FRGE-09 detected at 254 nm. Peak 1 = dihydroxybenzoic acid; Peak 2 = apigenin-6-C-glucoside; Peak 3 = luteolin-7-O-rutinoside; NI = not identified.

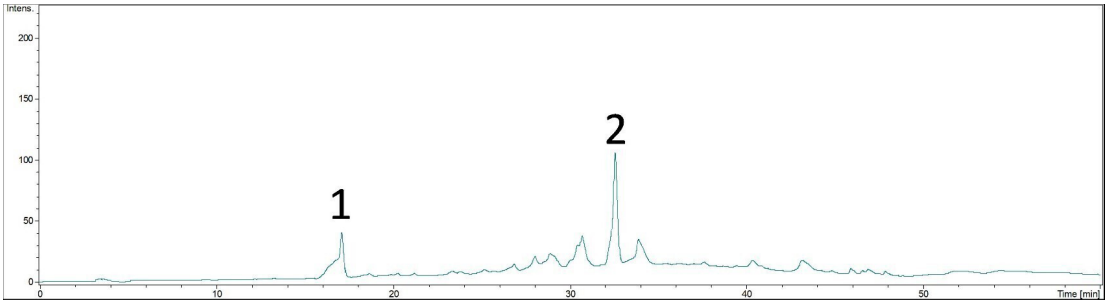
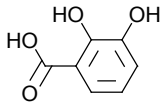
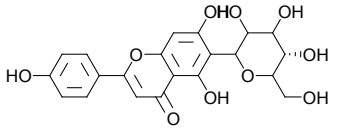
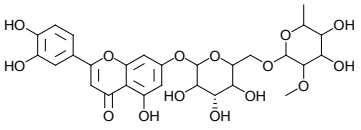


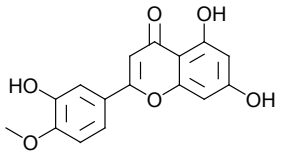
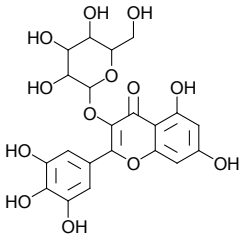
FIGURE 3 – HPLC chromatogram of FRGE-11 detected at 254 nm. Peak 1 = diosmetin; Peak 2 = myricetin-3-galactoside.

TABLE IV – Compounds identified in the FRGE-09 subfraction obtained from the chromatographic fractionation of the ethyl acetate fraction (EAF) of the lyophilized hydroethanolic extract of geopropolis (EHGV) by LC-ESI/IT-MS/MS

Peak	RT (min)	MW	$[M-H]^-$ m/z	MS/MS	Identification	Chemical structure
1	13.1	154	153	109	Dihydroxybenzoic acid	
2	23.2	432	431	311; 283	Apigenin-6-*C*-glucoside	
3	27.5	594	593	285	Luteolin-7-O-rutinoside	
4	47.8	599	599	463	NI	-

RT = Retention Time; MW = Molecular Weight; $[M - H]^-$ = Molecular Ion; MS = Mass Spectrometry. NI= not identified.

TABLE V - Compounds identified in the FRGE-11 subfraction obtained from the chromatographic fractionation of the ethyl acetate fraction (EAF) of the lyophilized hydroethanolic extract of geopropolis (EHGV) by LC-ESI/IT-MS/MS.

Peak	RT (min)	MW	$[M-H]^-$ m/z	MS/MS	Identification	Chemical structure
1	15.6	300	299	153	Diosmetin	
2	34.2	480	479	259; 237	Myricetin-3-galactoside	

RT = Retention Time; MW = Molecular Weight; $[M - H]^-$ = Molecular Ion; MS = Mass Spectrometry.

DISCUSSIONS

The present study demonstrates the cytotoxic activity of the FRGE-09 and FRGE-11 subfractions from the ethyl acetate fraction of *Melipona fasciculata* geopropolis against A549 and H460 lung cancer cell lines. These subfractions contained flavonoids, glycosylated flavonoids, and phenolic acids. The HF, EAF, and HMF fractions also inhibited proliferation in both cancer cell lines after 48 h, with HF showing the strongest effect (IC_{50} = 40.99 and 51.83 µg/mL), while EAF and HMF were active only at concentrations above 100 µg/mL.

The HF IC_{50} values observed here differ from those reported for geopropolis from *Melipona scutellaris* (9.55 µg/mL for H460) (Da Cunha *et al.*, 2013). Cytotoxicity values reported for hexane and ethyl acetate fractions of *Melipona mondury* geopropolis (IC_{50} = 24.24–46.62 µg/mL and 29.79–45.90 µg/mL, respectively) (Dos Santos *et al.*, 2017) were similar to those of HF from *M. fasciculata*, whereas EAF and HMF showed more distant results. Importantly, subfractions derived from EAF also contributed to the cytotoxic effects observed in both lung cancer cell lines.

No previous studies have described antitumor activity in H460 or A549 cells using subfractions obtained from liquid–liquid partitioning of *M. fasciculata* geopropolis. However, earlier research has shown anticancer activity of its hydroethanolic extract against canine osteosarcoma (Cinegaglia *et al.*, 2013), human laryngeal carcinoma (Bartolomeu *et al.*, 2016; Araújo *et al.*, 2015), and lung cancer cells (Barboza *et al.*, 2020), supporting the relevance of the present findings.

According to Table II, EAF, FRGE-9, and FRGE-11 showed significant selectivity indices (SI) for A549. Following Suffness (1990), SI ≥ 2 indicates greater toxicity toward tumor than normal cells, a criterion met by several fractions. FRGE-6 and FRGE-8 were twice as selective for H460 as for HUVEC, while FRGE-9 and FRGE-11 were three times more selective for A549.

The SI reported for the hexane fraction of *M. scutellaris* (SI ≈ 2 for H460) (Da Cunha *et al.*, 2013) was

lower than the SI obtained for HF in this study (> 6.09). Polyphenolic compounds identified in FRGE-9 and FRGE-11 included diosmetin, apigenin-6-C-glycoside, luteolin-7-O-rutinoside, myricetin-3-galactoside, and dihydroxybenzoic acid. Except for dihydroxybenzoic acid, previously reported in *M. fasciculata*, all other compounds are described here for the first time in this geopropolis.

Yin *et al.* (2009) demonstrated that treatment of IMR-90 lung cancer cells with dihydroxybenzoic acid reduced cell viability, induced DNA fragmentation, decreased mitochondrial membrane potential, and increased caspase-3 and caspase-8 activity. This compound also inhibited cell adhesion and reduced the production of VEGF, IL-6, IL-8, and ICAM-1.

Flavonoids exert anticancer effects through mechanisms that include modulation of carcinogen-metabolizing enzymes, induction of cell-cycle arrest, and activation of apoptosis, making them promising agents for lung cancer therapy (Hou & Kumamoto, 2010; Khan & Mukhtar, 2015; Braicu *et al.*, 2017). Apigenin-6-C-glycoside inhibited the growth of CORL-23 lung cancer cells (Conforti *et al.*, 2009), and Cao *et al.* (2016) reported that it selectively suppressed tumorsphere formation, migration, and invasion in lung cancer stem cells derived from H446 cells.

Chen *et al.* (2019) showed that diosmetin induced selective apoptotic death in A549 and H1299 lung cancer cells, without significant toxicity to normal cells. In vivo experiments demonstrated synergistic effects between diosmetin and paclitaxel, with no detectable toxicity to vital organs.

Luteolin is a multifunctional anticancer compound that suppresses proliferation, induces apoptosis, and inhibits migration in lung cancer cells. In A549 cells, its effects include activation of caspases 3 and 9, modulation of MEK, changes in Bcl-2 family protein expression, and regulation of ERK and Akt phosphorylation (Meng *et al.*, 2016). Suvarna *et al.* (2018) demonstrated that luteolin induces DNA damage, activates p53, triggers sustained JNK activation, and inhibits survival pathways, including PI3K/Akt, NF-κB, and MAPK. Zhang *et al.* (2024) showed that luteolin modulates the Akt/MDM2/p53 axis, enhancing p53 activation and suppressing proliferation and migration.

Myricetin also demonstrates potent anticancer activity. Zhang *et al.* (2014) found that myricetin enhanced radiosensitivity in A549 and H1299 cells, increasing apoptosis and caspase-3 expression. Shih *et al.* (2009) showed that myricetin inhibited adhesion, invasion, and migration in A549 cells by suppressing MMP-2 and uPA activity.

Although the antitumor activities of myricetin and luteolin are well documented, no previous study has reported antitumor activity for their glycosylated derivatives, luteolin-7-O-rutinoside and myricetin-3-galactoside. The presence of sugar moieties (rhamnose and galactose) may improve solubility, metabolic stability, and cellular transport (Chen *et al.*, 2020). Furthermore, glycosylated phenolic compounds may enhance caspase activation and modulate the p53 pathway, contributing to apoptosis (Thant *et al.*, 2024).

Overall, the results indicate that the antitumor activity of geopropolis fractions from *M. fasciculata* against A549 and H460 cells is associated with the presence of diosmetin, apigenin-6-C-glycoside, luteolin-7-O-rutinoside, myricetin-3-galactoside, and dihydroxybenzoic acid. These findings underscore the therapeutic potential of these constituents and highlight their promise as prototypes for future lung cancer treatments.

CONCLUSION

The FRGE-9 and FRGE-11 subfractions from the ethyl acetate fraction of the hydroethanolic extract of *Melipona fasciculata* geopropolis showed significant cytotoxicity against the A549 and H460 lung cancer cell lines. These subfractions contain dihydroxybenzoic acid, apigenin-6-C-glycoside, luteolin-7-O-rutinoside (FRGE-9), diosmetin, and myricetin-3-galactoside (FRGE-11), compounds associated with antitumor activity. Notably, diosmetin, apigenin-6-C-glycoside, luteolin-7-O-rutinoside, and myricetin-3-galactoside are reported here for the first time in *M. fasciculata* geopropolis.

Despite these promising findings, further cytotoxicity assays and mechanistic studies involving diosmetin, luteolin-7-O-rutinoside, and myricetin-3-galactoside are required to advance their potential development as prototype molecules for safer and more effective lung cancer therapies.

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DATA AVAILABILITY STATEMENT

All data is available within the article or its supplementary materials.

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